Amendments to the Specification:

Please replace paragraph [0008] with the following amended paragraph:

Drug therapies, using known active ingredients such as vasodilators, angiotensin II receptor antagonists, angiotensin converting enzyme inhibitors, diuretics, ~~antithrombolytic~~ anti-thrombotic agents, β-adrenergic receptor antagonsts, α-adrenergic receptor antagonists, calcium channel blockers, and the like, are available for treating heart failure and associated diseases. Of course, any drug used for treatment may result in side effects. For example, vasodilators may result in hypotension, myocardial infarction, and adverse immune response. Angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are often associated with acute renal failure, fetopathic potential, proteinuria, hepatotoxicity, and glycosuria as side effects. Similarly, common side effects associated with calcium channel blockers include hypotension, peripheral edema, and pulmonary edema. β-Adrenergic receptor antagonists and diuretics have been associated with incompatibility with nonsteroidal anti-inflammatory drugs in addition to impotence, gout, and muscle cramps in the case of diuretics and in addition to a decrease in left ventricular function and sudden withdrawal syndrome in the case of α-adrenergic receptor antagonists. Moreover, side effects associated with α-adrenergic receptor antagonists include thostatic hypotension, and side effects associated with ~~antithrombolytic~~ anti-thrombotic agents include excessive bleeding.

Please replace paragraph [0010] with the following amended paragraph:

The present invention provides methods for treating cardiovascular and related diseases, such as, for example, hypertrophy, hypertension, congestive heart failure, myocardial ischemia, ischemia reperfusion injuries in an organ, arrhythmia, and myocardial infarction. One embodiment is directed to a method of treating cardiovascular disease in a mammal by concurrently administering to the mammal a therapeutically effective amount of a combination of a compound suitable for use in methods of the invention and a therapeutic cardiovascular compound. Therapeutic cardiovascular compounds suitable for use in methods of the invention include an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, an ~~antithrombolytic~~ anti-thrombotic agent, a β-adrenergic receptor

antagonist, a vasodilator, a diuretic, an α-adrenergic receptor antagonist, an antioxidant, and a mixture thereof. In some embodiments, the therapeutic cardiovascular compound is PPADS.

Please replace paragraph [0076] with the following amended paragraph:

Pharmaceutically acceptable acid addition salts of compounds suitable for use in methods of the invention include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate, ~~n~~ N-methyl glutamine, etc., ~~(see, e.g.,~~ as disclosed for example by Berge et al. in their publication entitled Pharmaceutical Salts, in *J. Pharmaceutical Science*, 66: 1-19 (1977). Berge et al. outlined various potential useful salts along with their physicochemical studies, their bioavailabilities, their pharmacological studies and their toxicologies.

Please replace paragraph [0079] with the following amended paragraph:

Therapeutic cardiovascular compounds that may be concurrently administered with a compound suitable for use in methods of the invention include an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, an ~~antithrombolytic~~ anti-thrombotic agent, a β-adrenergic receptor antagonist, a vasodilator, a diuretic, an α-adrenergic receptor antagonist, an antioxidant, and a mixture thereof. A compound suitable for

use in methods of the invention also may be concurrently administered with PPADS (pyridoxal phosphate-6-azophenyl-2',4'-disulphonic acid), also a therapeutic cardiovascular compound, or with PPADS and another known therapeutic cardiovascular compound as already described. In a preferred embodiment, pyridoxal-5'-phosphate is concurrently administered with PPADS or with PPADS and another known therapeutic cardiovascular compound, preferably an angiotensin converting enzyme inhibitor or an angiotensin II receptor antagonist.

Please replace paragraph [0082] with the following amended paragraph:

For example, myocardial ischemia may be treated by the administration of, for example, angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, an ~~antithrombolytic~~ anti-thrombotic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, or a mixture thereof. In some instances, congestive heart failure may be treated by the administration of, for example, angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, a vasodilator, a diuretic, or a mixture thereof.

Please replace paragraph [0083] with the following amended paragraph:

Myocardial infarction may be treated by the administration of, for example, angiotensin converting enzyme inhibitor, a calcium channel blocker, an ~~antithrombolytic~~ anti-thrombotic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, or a mixture thereof.

Please replace paragraph [0086] with the following amended paragraph:

~~Antithrombolytic~~ Anti-thrombotic agents are used for reducing or removing blood clots from arteries.

Please replace paragraph [0092] with the following amended paragraph:

~~Antithrombolytic~~ Anti-thrombotic agents known in the art include antiplatelet agents, aspirin, and heparin.

Please replace paragraph [0126] with the following amended paragraph:

Example 9: In Vitro - Ischemia Reperfusion in Isolated Rat Hearts and Measurement of Left Ventricular Developed Pressure (LVDP)

Male Sprague-Dawley rats weighing 250-300g are anaesthetized with a mixture of ketamine (60 mg/kg) and xylazine (10 mg/kg). The hearts are rapidly excised, cannulated to a Langendorff apparatus and perfused with Krebs-Henseleit-solution, gassed with a mixture of 95% O_2~~2~~ and 5% CO_2~~2~~, pH 7.4. The perfusate contained (in mM): 120 NaCl, 25 $NaHCO_3$~~3~~, 11 glucose, 4.7 KCl, 1.2 KH_2~~2~~$PO_4$4, 1.2 $MgSO_4$4 and 1.25 $CaCl_2$~~2~~.

Please replace paragraph [0127] with the following amended paragraph:

The hearts are electrically stimulated at a rate of 300 beats/min (Phipps and Bird Inc., Richmond, VA) and a water-filled latex balloon is inserted in the left ventricle and connected to a pressure transducer (Model 1050BP; BYOPAC SYSTEM INC., Goleta, California) for the left ventricular systolic measurements. The left ventricular end diastolic pressure (LVEDP) is adjusted at 10 mmHg at the beginning of the experiment. In some experiments the left ventricular pressures are differentiated to estimate the rate of ventricular contraction (+dP/dt) and rate of ventricular relaxation (-dP/dt) using the Acknowledge 3.03 software for Windows (BIOPAC SYSTEM INC.,) Goleta, California). All hearts are stabilized for a period of 30 min and then randomly distributed into nine different experimental groups (n= 5-8 per group). The experimental groups are defined as follows:

1) Control group (control hearts are further perfused for 90 minutes for a total of 130 min of continuous perfusion);
2) Ischemia reperfusion group (Ischemia reperfusion hearts are made globally ischemic by stopping the coronary flow completely for 30 min and then the hearts are reperfused for 60 min);
3) P-5-P (15 ~~u~~μM) treated group;
4) captopril (100 ~~u~~μM) treated group;

5) verapamil (0.01 ~~u~~μM)) treated group;

6) propranolol (3mM) treated group;

7) PPADS (10 ~~u~~μM) treated group;

8) P-5-P + captopril treated group;

9) P-5-P + verapamil treated group;

10) P-5-P + propranolol treated group;

11) P-5-P + PPADS treated group.

Please replace paragraph [0129] with the following amended paragraph:

Hearts subject to 30 min of ischemia followed by 60 min of reperfusion showed slight recovery in the contractile function as represented by 29.5% recovery in LVDP (left ventricular developed pressure). As compared to the untreated group, treatment with P-5-P, captopril, or P-5-P and captopril showed better recoveries in LVDP by 78.2%, 61.4%, and 132% respectively (Table I).

Table I

Effect of Pyridoxal-5-phosphate (P-5-P, 15~~u~~μM) and Captopril (100~~u~~μM) on % recovery of left ventricular systolic pressure (LVDP).

Drugs	LVDP		LVEDP	LVSP	% recovery
	(B)	*(A)*	*mmHg*	*mmHg*	(LVDP)
Untreated	87±7	25±2.9	62±5.6	87±6.9	29.5±3.7
P5P	80±3.8	63±5	35±4.8	98±8.2	78.2 ± 3.3*
Captopril	78±10.9	47±8.6	54±6.7	101±14.6	61.4 ± 5.2*
P5P + Captopril	89±6.9	69±7.4	28±7.3	117±8.4	132 ± 7.5#

(A) =After ischemia, *(B)* =Before ischemia.

Please replace paragraph [0130] with the following amended paragraph:

Hearts subject to 30 min of ischemia followed by 60 min of reperfusion showed slight recovery in the contractile function as represented by 29.5% recovery in LVDP. As compared to the untreated group, treatment with P-5-P, verapamil, or P-5-P and verapamil showed better recoveries in LVDP by 78.2%, 43%, and 109% respectively (Table II).

Table II

Effect of Pyridoxal-5-phosphate (P-5-P,15~~u~~μM) and Verapamil (0.01~~u~~μM) on % recovery of left ventricular systolic pressure (LVDP).

Drugs	**LVDP**		**LVEDP**	**LVSP**	**% recovery**
	(B)	*(A)*	*mmHg*	*mmHg*	(LVDP)
Untreated	87±7	25±2.9	62±5.6	87±6.9	29.5±3.7
P5P	80±3.8	63±5	35±4.8	98±8.2	78.2 ± 3.3*
Verapamil	54±9.1	23±4.5	55±5.1	78±7.7	43 ± 6.6
P5P + Verapamil	78±10.5	85±11.7	34±7.3	119±8	109 ± 4.6#

(A) =After ischemia, *(B)* =Before ischemia.

Please replace paragraph [0131] with the following amended paragraph:

Hearts subject to 30 min of ischemia followed by 60 min of reperfusion showed slight recovery in the contractile function as represented by 29.5% recovery in LVDP. As compared to the untreated group, treatment with P-5-P, PPADS, or P-5-P and PPADS showed better recoveries in LVDP by 78.2%, 61%, and 128% respectively (Table III).

Table III

Effect of Pyridoxal-5-phosphate (P-5-P,15~~u~~μM) and Pyridoxal phosphate 6-azophenyl-2'-4'disulfonic acid (PPADS 100~~u~~μM) on % recovery of left ventricular systolic pressure (LVDP).

Drugs	**LVDP**		**LVEDP**	**LVSP**	**% recovery**
	(B)	*(A)*	*mmHg*	*mmHg*	(LVDP)
Untreated	87±7	25±2.9	62±5.6	87±6.9	29.5±3.7

P5P	80±3.8	63±5	35±4.8	98±8.2	78.2 ± 3.3*
PPADS	92±15.2	58±13.6	57±6.3	115±11.5	61 ± 4.8*
P5P + PPADS	82±15.8	105±22.8	34±3.1	139±21.6	128 ± 13.8#

(A) =After ischemia, *(B)* =Before ischemia.

Please replace paragraph [0132] with the following amended paragraph:

Hearts subject to 30 min of ischemia followed by 60 min of reperfusion showed slight recovery in the contractile function as represented by 29.5% recovery in LVDP. As compared to the untreated group, treatment with P-5-P, propranolol, or P-5-P and propranolol showed better recoveries in LVDP by 78.2%, 74%, and 120% respectively (Table IV).

Table IV

Effect of Pyridoxal-5-phosphate (P-5-P,15~~u~~µM) and Propranolol (3~~u~~µM) on % recovery of left ventricular systolic pressure (LVDP).

Drugs	**LVDP**		**LVEDP**	**LVSP**	**% recovery**
	(B)	*(A)*	*mmHg*	*mmHg*	(LVDP)
Untreated	87±7	25±2.9	62±5.6	87±6.9	29.5±3.7
P5P	80±3.8	63±5	35±4.8	98±8.2	78.2 ± 3.3*
Propranolol	61±10.8	45±9.7	27±6.6	72±15.1	74 ± 4.9*
P5P + Propranolol	67±12.6	75±10.4	40±4.2	115±8.3	120 ± 15.5#

(A) =After ischemia, *(B)* =Before ischemia

Please replace paragraph [0135] with the following amended paragraph:

Example 10: In Vivo - Coronary Artery Ligation

Myocardial infarction is produced in male Sprague-Dawley rats (200-250 g) by occlusion of the left coronary artery as described in Sethi et al., J. Cardiac Failure, 1(5) (1995) and Sethi et al., Am. J. Physiol., 272 (1997). The animals were anesthetized with ether, the skin incised along the left sternal border, the fourth rib cut proximal to the sternum, and retractors inserted.

The pericardial sac was perforated and the heart was exteriorized through the intercostal space. The left coronary artery was ligated about 2 mm from its origin with a 6-0 silk suture and the heart was repositioned in the chest. Throughout the course of the operation, the rats were maintained on a positive pressure ventilation delivering a mixture of 95% O_2 and 5% CO_2 mixed with ether.

Please replace paragraph [0145] with the following amended paragraph:

In addition to captopril, other angiotensin converting enzyme inhibitors, such as, for example, enalapril or imidapril, can similarly be administered in place of captopril. In addition to verapamil, other known calcium channel blockers, such as, for example, nifedipine or diltiazem, can similarly be administered in place of verapamil. In addition to propranolol, other β-adrenergic receptor antagonists such as, for example, atenolol, timolol, and metoprolol can similarly be administered in place of propranolol. In addition to aspirin, other ~~antithrombolytic~~ anti-thrombotic agents such as, for example, antiplatelet agents and heparin can similarly be administered in place of aspirin. Additionally, angiotensin II receptor antagonists such as, for example, losartan and valsartan can be used in the above example.

Please replace paragraph [0155] with the following amended paragraph:

In addition to captopril, other angiotensin converting enzyme inhibitors, such as, for example, enalapril or imidapril, can similarly be administered in place of captopril. In addition to verapamil, other known calcium channel blockers, such as, for example, nifedipine or diltiazem, can similarly be administered in place of verapamil. In addition to propranolol, other β-adrenergic receptor antagonists such as, for example, atenolol, timolol, and metoprolol can similarly be administered in place of propranolol. In addition to aspirin, other ~~antithrombolytic~~ anti-thrombotic agents such as, for example, antiplatelet agents and heparin can similarly be administered in place of aspirin. Additionally, angiotensin II receptor antagonists such as, for example, losartan and valsartan can be used in the above example.

Please replace paragraph [0156] with the following amended paragraph:

Example 12: In Vivo - Hypertension

It has been well demonstrated by various investigators that feeding 8-10% sucrose in water induces hypertension in rats. Zein et al., in their publication entitled Sugar-Induced Blood Pressure Elevations Over the Lifespan of Three Substrains of Wistar Rats in Am. Coll. Nutr., 17 (1), 36-37, 1998, have shown that high dietary sucrose can chronically increase systolic blood pressure (SBP) in three substrains of Wistar rats. Increased concentrations of circulating insulin were found in Wistar Kyoto rats and Munich Wistar rats suggesting that the glucose/insulin system was involved, at least in these two substrains, in the maintenance of high SBP levels during chronic, heavy sugar ingestion.; Hulman et al. in their publication entitled The Effect of Excess Dietary Sucrose on Growth, Blood Pressure, and Metabolism in Developing Sprague-Dawley Rats in Pediatr. Res., 36:95-101, have shown that consumption of a diet in which complex carbohydrate has been replaced by sucrose causes both elevated blood pressure and insulin resistance in juvenile rats with no genetic predisposition in either condition. Although blood pressure increased with increasing age and body weight in all four diet groups, higher blood pressures were clearly correlated with the sucrose diet in both males and females. The higher blood pressure cannot be explained by greater total body weight in the sucrose-fed animals, because there was no difference in weight between control-fed and sucrose-fed rats in each sex group.; Reaven et al., in their publication entitled Sugar-Induced Hypertension in Sprague-Dawley Rats in Am. J. Hypertens; 1991:610-614, have shown that the ability of simple sugars to increase plasma insulin and TG concentration and raise blood pressure is not unique to fructose, but can also be seen when Sprague-Dawley rats eat diets enriched with either glucose or sucrose. Since plasma glucose concentrations did not change, it is assumed that glucose-fed and sucrose-fed Sprague-Dawley rats also became more resistant to insulin-stimulated glucose uptake. In applying this model, the concurrent administration of pyridoxal-5'-phosphate and captopril or verapamil significantly decreases the sucrose-induced increase in systolic blood pressure (SBP).

Please delete paragraph [00166].

~~All references, applications, and patents cited herein are incorporated by reference.~~